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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/510,560	02/22/2000	Kenneth Iain Cumming	00.1090.US	3011

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EXAMINER	
LUNDGREN, JEFFREY S	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/510,560	CUMMING ET AL.	
	Examiner	Art Unit	
	JEFFREY LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/6/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *178,182-198,202-214 and 222-257* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251 and 253-256* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 25,189-195,197,207,210,229-235,237,239,241-243,247-249 and 252.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A Request for Continued Examination under 37 CFR § 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on November 6, 2007, has been entered.

Claims 178, 182-198, 202-214 and 222-257, are pending in the instant application; claims 189-195, 197, 207, 210, 229-235, 237, 239, 241-243, 247-249, 252 and 257, are withdrawn from consideration; and claims 178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251 and 253-256, are the subject of the Office Action below.

Previous Rejections Withdrawn

Any previous rejections not reiterated in the instant Office Action are considered withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251 and 253-256, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the introduction of new matter. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Independent claims 178, 211, 240 and 246, recite the phrase "compressible blend" which constitutes new matter. Although Applicants' specification supports the phrase "compressed

blend" the former phrase is much broader and only relates to a property. For example, Applicants do not disclose a mixture in a solid oral dosage form that is capable of being compressed, yet is not compressed. However, the claims currently read on such a form. Correction is required.

Independent claims 178, 211, 240 and 246, recite "the only component of the dosage form that enhances absorption of the drug across said epithelial cell lining." Although Applicants have support for a solid dosage form that comprises a "single absorption enhancer," Applicants do not have adequate support for the currently claimed phrase. For example, see paragraph 0030 of Applicants' disclosure where solid oral dosage forms comprising one or more enhancers are disclosed. Applicants have not reasonably described their invention to exclude other components that would have an enhancing effect.

Claims 253-256 are rejected because new matter is introduced by the claim requiring all components of the dosage form to be solid at room temperature. The specification lacks adequate support for these limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 178, 182-188, 196, 198, 202-206, 208, 209, 211-214, 222-228, 236, 238, 240, 244-246, 250, 251 and 253-256, are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts *et al.*, International Patent Application Publication WO 97/05903, published on February 20, 1997, in view of Heiber *et al.*, U.S. Patent No. 5,346,701, issued on September 13, 1994, and optionally any one or more of the following of: Teng *et al.*, U.S. Patent No. 6,747,014 B2, issued on June 8, 2004; Garces *et al.*, U.S. Patent No. 5,736,161, April 7, 1998; and Bachynsky *et al.*, U.S. Patent No. 5,190,748, issued on March 2, 1998.

Claim 178 is directed towards a solid oral dosage form which is effective in delivering a drug and an enhancer, each as defined below, to epithelial cells lining an intestine comprising:

(1) a compressible blend of:

(A) a therapeutically effective amount of a hydrophilic or macromolecular drug in the form of crystalline and/or amorphous particles, in admixture with

(B) an absorption enhancer which: (i) is a solid at room temperature; (ii) is a salt of a medium chain fatty acid having a carbon chain length of from 8 to 14 carbon atoms in particulate form and (iii) is present in the dosage form in a therapeutically effective amount and such that the ratio of the drug to the enhancer is 1:100,000 to 10:1, and

(2) a delayed release polymer coating,

wherein the salt of the medium chain fatty acid is the only component of the dosage form that enhances absorption of the drug across said epithelial cell lining. Claims 211, 240 and 246 are similar.

Watts discloses a drug delivery composition (tablet, capsule, including a gelatin capsule, and a pellet) for drug delivery through oral administration (see Abstract; accordingly this is a delayed release formulation) comprising a drug (*e.g.*, polypeptide and polysaccharide including heparin and low molecular weight heparin (meets the drug limitations of claims 182-186, 196, 208, 209, 222, 224, 225, 226, 236, 244, 245, 250, 251); see page 8), and an absorption promoter (see page 24; see also Example 10 on page 22 of the PCT). This formulation is a solid at room temperature, as is the enhancer sodium caprate and capric acid. It is also provided with the auxiliary excipient Labrasol, and without Labrasol, which instead of being an enhancer is

considered a dispersing agent (see Detailed Description, see also Example 1-3 on pages 16-18). Watts also teaches the use of a single enhancer with insulin and capric acid (see Figure 3, and description thereof). Watts teaches that the absorption promoter comprises a fatty acid or a salt thereof, where the fatty acid has between 6 and 16 carbon atoms, for example capric acid (Example 10) or its sodium salt, sodium caprate (pages 5, 24, claims 1 and 3) which can be used *alone* or in admixture with a fatty acid derivative (e.g. mono/diglycerides: see pages 5-7) to obtain synergy (meets the enhancer limitations of claims 182, 187, 188, 198, 222, 223, 227, 228, 238). For example, Watts states:

> "***It has been known for some time that sodium caprate can act as an absorption promoting agent***, probably by the perturbation of membranes or modification of tight junctions between cells (Kajii et al. J. Pharm. Sci. 77 390, 1988)."

Watts, paragraph bridging pages 2 and 3 (emphasis added).

Watts further teaches that the drug can be chosen from heparin and LMWH, and more (pages 8, 11-12, and 24; and claim 6). Watts teaches that the composition is formulated in a capsule (*e.g.*, hard/soft gelatin), tablet, pellet, or multiparticulate capsule or tablet which is comprised of or coated with a material which is dissolved by the conditions found in the intestines such as "rate-controlling" being sustained release and/or enteric release, such as a cellulose ester, HPMC at page 9, lines 14-29 (as in claim 202), or a methacrylic acid polymer at pages 10-12 (as in claims 204, 213, 214), for *in vivo* therapeutic administration to a patient (see pages 14-15). Such enteric coatings meet the limitations of being a "rapid onset dosage form" as in claim 203 (compare to paragraph 0037 of Applicants' disclosure, *i.e.*, "releases the drug and the enhancer *rapidly* once the *appropriate* site in the intestine has been reached"). Watts teaches sodium caprate and capric acid; both components prepared in a formulation similar to Example 3 would result in all components being a solid at room temperature as required by claims 253-256.

Although Watts teaches tablet dosage forms as well as preparing certain formulations by adding certain mass amounts of active and enhancer, Watts does not explicitly state that the active agent nor the enhancer are provided in the form of particles.

Heiber teaches certain formulations that are pressed into tablet form from a dry blend of LMWH and an enhancer (*i.e.*, NaTC):

> "LMWH tablets are prepared in the following manner. ***An active LMWH layer was prepared by dry blending 2.010 g LMWH***, 0.504 g of hydroxypropyl cellulose, (KLUCEL LF) ***and 0.450 g of NaTC***. To this was added 500 µl of 200 proof ethanol and the mixture was wet blended to give a wet granulation having a dough like consistency. The wet granulation was passed through an 18 mesh screen and allowed to dry for 3 hours in a draft oven at 25 °C. The dried granulation was then passed through a 20 mesh screen and placed in a glass vial with 0.030 g of magnesium stearate and 0.006 g of mint flavor and dry blended again. A 100 mg amount of this mixture was filled into a 1/2" diameter die and ***precompressed*** on a Carver Press Model C ***with 0.25 ton pressure*** for a 3 second time dwell time to form the active drug/enhancer/polymer layer."

Heiber, col. 10, lines 25-41. Such a teaching meets the physical form limitations of the independent claims, and claim 205, 206, 212.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Watts and Heiber are directed toward providing pharmaceutical dosage forms, such as tablets, for administering pharmaceutically active peptides that have poor absorption characteristics. Watts clearly shows that an oral dosage form comprising insulin has a much increased bioavailability in the presence of the caprate anion in the GIT, and suggests a number of active peptides that this approach is useful for, including LMWH in the form of a tablet, and specifically with sodium caprate as the enhancer. Heiber teaches a particular tablet formulation that is prepared as a dry blend of LMWH and enhancer particles and is compressed to have a particular tablet shape and size. Although Watts does not explicitly teach a dry blend compression tablet, and Heiber does not teach sodium caprate, arriving at an oral tablet for GIT delivery in the claimed physical form would have been obvious in view Watts and Heiber because the differences between what is claimed and what is taught by Watts and Heiber is considered well-known in the art and/or routine. For example, see Teng, where a pharmaceutical composition of a pressed tablet is prepared from a powder composition of particles comprising sodium caprylate used as an enhancer for improved absorption of an active agent (*i.e.*, an oligonucleotide; Example 15). See Garces, wherein an oral capsule is prepared with LMWH and sodium caprate, and therefore has increased absorption (Example 2). Bachynsky further demonstrates these points, as it is taught that the claimed active agents may take the form of the a liquid formulation or numerous solid formulations (including enterically-

coated tablets; see col. 8, lines 18-50), and may have multiple approaches for delivery through various mucosal membranes, such as oral or rectal administration. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JSL/

/Jon D. Epperson/
Primary Examiner, AU 1639